REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

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1. REPORT DATE *(DD-MM-YYYY)*	2. REPORT TYPE	3. DATES COVERED *(From - To)*
2008	Journal Article-Am.J of Physiology	

4. TITLE AND SUBTITLE

Cerebrovascular Responses to Incremental Exercise During Hypobaric Hypoxia: Effect of Oxygenation on Maximal Performance

5a. CONTRACT NUMBER

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Thermal and Mountain Medicine Division
U.S. Research Institute of Environmental Medicine
Natick, MA 01760-5007

8. PERFORMING ORGANIZATION REPORT NUMBER

M07-58

9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)

Same as #7 above.

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT

Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

While performing demanding physical activity for long durations, fluid and electrolyte imbalance is common in athletes, military personnel, and recreational hikers. The military and civilian communities have introduced extensive heat mitigation measures to manage heat strain and reduce the risk of serious exertional heat illnesses (EHI). These heat mitigation measures include fluid and electrolyte replacement guidelines, vigilance, and identifying high-risk individuals. Despite these measures, exercise in hot weather continues to result in preventable injuries and deaths in young, healthy individuals. With existing emphasis on appropriate fluid intake during exercise for the avoidance of dehydration, heat illness, and associated performance decrements, there has been a subsequent increase in reported exertional hyponatremia (HYPO) cases related to excessive water intake, elevated sweating rates, excessive sodium losses in sweat, and inadequate sodium intake in soldiers (1), athletes (2,3,4), and recreational hikers (5,6). The primary purpose of this article is to systemically examine the epidemiological literature of fluid and electrolyte imbalances that occur during physical activity. The secondary purpose of this article is to examine signs and symptoms of HYPO and EHI cases

15. SUBJECT TERMS

altitude; near infrared spectroscopy; cerebral blood flow; fatigue; muscle oxygenation

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(Include area code)*
Unclassified	Unclassified	Unclassified	Unlimited	8	

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Am J Physiol Heart Circ Physiol 294: H164–H171, 2008.
First published November 21, 2007; doi:10.1152/ajpheart.01104.2007.

Cerebrovascular responses to incremental exercise during hypobaric hypoxia: effect of oxygenation on maximal performance

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Submitted 24 September 2007; accepted in final form 19 November 2007

Subudhi AW, Lorenz MC, Fulco CS, Roach RC. Cerebrovascular responses to incremental exercise during hypobaric hypoxia: effect of oxygenation on maximal performance. *Am J Physiol Heart Circ Physiol* 294: H164–H171, 2008. First published November 21, 2007; doi:10.1152/ajpheart.01104.2007.—We sought to describe cerebrovascular responses to incremental exercise and test the hypothesis that changes in cerebral oxygenation influence maximal performance. Eleven men cycled in three conditions: *1*) sea level (SL); *2*) acute hypoxia [AH; hypobaric chamber, inspired P_{O_2} ($P_{I_{O_2}}$) 86 Torr]; and *3*) chronic hypoxia [CH; 4,300 m, $P_{I_{O_2}}$ 86 Torr]. At maximal work rate ($\dot{W}_{max}$), fraction of inspired oxygen ($F_{I_{O_2}}$) was surreptitiously increased to 0.60, while subjects were encouraged to continue pedaling. Changes in cerebral (frontal lobe) (C_{OX}) and muscle (vastus lateralis) oxygenation (M_{OX}) (near infrared spectroscopy), middle cerebral artery blood flow velocity (MCA V_{mean}; transcranial Doppler), and end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) were analyzed across $\%\dot{W}_{max}$ (significance at $P < 0.05$). At SL, $P_{ET_{CO_2}}$, MCA V_{mean}, and C_{OX} fell as work rate rose from 75 to 100% $\dot{W}_{max}$. During AH, $P_{ET_{CO_2}}$ and MCA V_{mean} declined from 50 to 100% $\dot{W}_{max}$, while C_{OX} fell from rest. With CH, $P_{ET_{CO_2}}$ and C_{OX} dropped throughout exercise, while MCA V_{mean} fell only from 75 to 100% $\dot{W}_{max}$. M_{OX} fell from rest to 75% $\dot{W}_{max}$ at SL and AH and throughout exercise in CH. The magnitude of fall in C_{OX}, but not M_{OX}, was different between conditions (CH > AH > SL). $F_{I_{O_2}}$ 0.60 at $\dot{W}_{max}$ did not prolong exercise at SL, yet allowed subjects to continue for 96 ± 61 s in AH and 162 ± 90 s in CH. During $F_{I_{O_2}}$ 0.60, C_{OX} rose and M_{OX} remained constant as work rate increased. Thus cerebral hypoxia appeared to impose a limit to maximal exercise during hypobaric hypoxia ($P_{I_{O_2}}$ 86 Torr), since its reversal was associated with improved performance.

altitude; near infrared spectroscopy; cerebral blood flow; fatigue; muscle oxygenation

CEREBRAL HYPOXIA HAS BEEN proposed to be a critical factor limiting exercise performance (37), particularly in hypoxia (7), yet little evidence exists to directly support this theory. Kayser et al. (31) were the first to show that rapidly increasing the fraction of inspired oxygen ($F_{I_{O_2}}$) at the point of maximal exertion prolonged exercise in hypoxia-acclimatized subjects. They concluded that the effect of increased $F_{I_{O_2}}$ was too quick to have reversed metabolic factors associated with peripheral (intramuscular) fatigue and suggested that cerebral reoxygenation was a more likely explanation for the improvement in exercise performance. Calbet et al. (11) arrived at similar conclusions after using a comparable model to study factors limiting O_2 uptake ($\dot{V}_{O_2}$). They suggested that exercise under hypoxic conditions may have presented a significant threat to cerebral oxygenation; thus cardiac and/or motor output was curtailed to maintain favorable tissue oxygenation status. While these studies insinuate the importance of preserving cerebral oxygenation during exercise in hypoxia, the conclusions remain speculative, since neither cerebral oxygenation nor cerebral blood flow was measured.

Rasmussen et al. (40) have shown that decreased cerebral oxygenation was associated with a loss of handgrip strength during severe, acute hypoxia (AH) [$F_{I_{O_2}}$ 0.10; inspired P_{O_2} ($P_{I_{O_2}}$) 71 Torr; arterial O_2 saturation from pulse oximetry (Sp_{O_2}) ~82%], and Amann et al. (4) confirmed that, under severe hypoxic conditions ($F_{I_{O_2}}$ 0.10; $P_{I_{O_2}}$ 69 Torr; Sp_{O_2} ~67%), increasing $F_{I_{O_2}}$ at the point of exercise task failure improved cerebral oxygenation and prolonged cycling time to exhaustion, yet such effects were not seen during more moderate levels of hypoxia ($F_{I_{O_2}}$ 0.15; $P_{I_{O_2}}$ 104 Torr; Sp_{O_2} ~82%). It has thus been suggested that cerebral hypoxia plays a dominant role in limiting exercise performance when arterial P_{O_2} falls below a critical level (4). However, the role of cerebral blood flow and its contribution to the development of cerebral hypoxia during maximal exercise have not been described.

Arterial CO_2 pressure (Pa_{CO_2}) is believed to be the dominant factor regulating cerebral blood flow under normoxic and hypoxic conditions (9). During intense exercise, reduced Pa_{CO_2} due to relative hyperventilation results in cerebral vasoconstriction and decreased cerebral blood flow and thus may be responsible for a slight decrease in cerebral oxygenation near maximal exercise under normoxic conditions (6, 46). It follows that, during intense hypoxic exercise, increased ventilation (27) may cause an even larger fall in Pa_{CO_2}, which could impose cerebral hypoxia of sufficient severity to limit maximal exercise performance.

We tested this hypothesis during incremental exercise to maximal exertion, in combination with the gas switch model of Kayser et al. (31) under normoxic and both AH and chronic hypoxic (CH) conditions. We reasoned that, if cerebral hypoxia exerts a large influence on maximal exercise performance, the switch to hyperoxic gas would improve performance via a reversal of cerebral deoxygenation (35).

METHODS

Institutional approval was granted by the participating institutions before subject recruitment. Eleven active-duty, male military subjects were recruited from the Human Research Volunteer program at the US Army Natick Soldier Research, Development, and Engineering Center (Natick, MA). All gave their written, informed, voluntary consent to participate. Subjects were sea level (SL) residents with no exposure to altitudes >500 m during the previous 3 mo and were given medical clearance before participation.

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Study outline. The protocol presented represents a portion of a larger Army medical research project conducted under the direction of the United States Army Research Institute of Environmental Medicine (USARIEM). Subjects were first studied at SL in the USARIEM laboratories ($P_{I_{O_2}}$ 149 Torr) to obtain baseline measurements. During the SL phase, ~1 wk after baseline was established, the effects of AH were determined during a 1-h exposure to hypobaric hypoxia ($P_{I_{O_2}}$ 86 Torr) in the USARIEM environmental chamber. Approximately 7 wk later, subjects were flown to moderate altitude for a 5-day acclimatization period at the United States Air Force Academy in Colorado Springs, CO ($P_{I_{O_2}}$ 115 Torr). Subjects were then driven to the USARIEM high-altitude laboratory on the summit of Pike's Peak ($P_{I_{O_2}}$ 86 Torr) and retested after 24 h (CH).

Exercise protocol. All subjects performed four incremental exercise bouts to maximal volitional exhaustion on an electrically braked cycle ergometer (Lode, Excalibur Sport). The first test was used as a practice session to familiarize subjects with the protocol and instrumentation. The remaining three experimental trials were performed under similar conditions at SL, AH (hypobaric chamber), and CH. After a 3-min rest period on the ergometer, pedaling was initiated at 50 W with a target rate of 85 rpm. Work rate was increased to 100, 130, and 160 W in 2-min increments. Thereafter, work rate was adjusted by 15 W each minute until exhaustion. When criteria for maximal aerobic power ($\dot{W}_{max}$) were achieved [respiratory exchange ratio > 1.10, no increase in $\dot{V}_{O_2}$ over the previous 15 s, pedal cadence dropping below 60 rpm (70% of target rpm), despite strong verbal encouragement], the inspired $F_{I_{O_2}}$ was surreptitiously switched to 0.60 (single blind design), while verbal support was continued. The test was terminated when cadence could not be maintained above 50 rpm (60% of target rpm). Power ($\dot{W}$) was interpolated between stages as $\dot{W}$ = work rate of last stage completed + [(work rate increment) × (time into current stage/duration of stage in seconds)]. $\dot{W}_{max}$ was calculated with the same formula, provided that subjects completed at least 15 s of the stage. Reliability of metabolic and power parameters determined by similar methods has been described in a previous report (5).

Instrumentation. A continuous-wave near infrared spectrometer (NIRS; Oxymon MKII, Artinis) was used to monitor changes in cerebral and muscle oxygenation throughout exercise. The theory, limitations, and reliability of measurements obtained with this instrument during incremental exercise have been previously reported (46). During all exercise sessions, subjects were instrumented with two pairs of NIRS probes to monitor absorption of light across cerebral and muscle tissue. Headsets were constructed to hold one near infrared emitter and detector pair over the left frontal cortex region of the forehead. Spacing between optodes was 4.5 cm, and headset sizing and placement were adjusted and recorded to ensure optimal signal strength on each individual during each trial. A second emitter and detector pair was affixed over the belly of the left vastus lateralis muscle. Placement of the optodes was measured (~15 cm above the proximal border of the patella and 5 cm lateral to the midline of the thigh), marked with indelible ink, and recorded to facilitate subsequent replacements. Skinfold measurements were made in the sagittal plane midway between optodes to account for skin and adipose thickness. Probes were held in place by a plastic spacer with an optode distance of 5.0 cm and secured to the skin using double-sided tape. Elastic bandages were used to shield optodes from ambient light. A modified form of the Beer-Lambert Law was used to calculate micromolar changes in tissue oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb) across time using received optical densities from two continuous wavelengths of near infrared light (780 and 850 nm) and published differential path-length factors of 4.95 (15) and 5.93 (48) for muscle and cerebral tissue, respectively. Changes in total Hb (THb) were calculated by the sum of HbO_2 and HHb and used as an index of change in regional blood volume (47). All cerebral and muscle measurements were normalized to reflect changes from a 1-min baseline period immediately before the beginning of the exercise protocol (arbitrarily defined as 0 μM) to express the magnitudes of changes throughout exercise. Data were recorded at 125 Hz and filtered with a Bartlett Triangle smoothing algorithm before analysis.

Transcranial Doppler was used to monitor middle cerebral artery (MCA) blood flow velocity (V_{mean}) during exercise. The custom-made NIRS headsets were modified to hold a 2-MHz Doppler probe (DWL Multi Dop T2) over the temporal window to insonate the artery (34). All measurements were optimized at the same penetration depth (42–48 mm) on each individual by a single, trained investigator. Continuous tracings of the velocity envelope were recorded at 125 Hz and processed offline to determine time-averaged velocity (MCA V_{mean}). It was assumed that MCA V_{mean} measurements were reflective of changes in cerebral blood flow throughout the protocol, based on data showing consistent MCA diameter across a range of Pa_{CO_2} values (19, 45) and parallel increases in internal carotid artery flow and MCA V_{mean} during incremental exercise (23).

Respiratory and metabolic measurements of ventilation, $\dot{V}_{O_2}$, and CO_2 production were obtained over 15-s periods via an automated metabolic cart (ParvoMedics TrueOne 2400, Sandy, UT) following correction for small volumes drawn (300 ml/min) into a separate CO_2 analyzer (Beckman LB2) for end-tidal P_{CO_2} ($P_{ET_{CO_2}}$) determinations. Inspired air was directed to the subject through 1.8 m of plastic tubing and valve system that delivered either ambient air or compressed, medical grade, dry gas (60% O_2, 40% N_2) via a 200-liter Douglas bag reservoir. Heart rate was measured and recorded with a chest strap and monitor (Polar USA, Irvine, CA). Subjects were instructed to keep their hands and fingers relaxed during exercise testing to obtain strong, pulsatile, finger-tip Sp_{O_2} measurements from either the left index or middle finger using a Nellcor N-200 oximeter (Pleasanton, CA). The instrument is accurate to ±2 units across the range of 70–100% and demonstrates acceptable resilience to motion artifact (32).

Analyses. Continuous data were collapsed to analyze specific time points of interest, corresponding to rest and 25, 50, 75, and 100% of $\dot{W}_{max}$ while breathing ambient air, plus at $\dot{W}_{max}$ obtained after administration of 60% O_2 (+O_2). Metabolic data after the gas switch to $F_{I_{O_2}}$ 0.60 were not analyzed because several subjects reached exhaustion before adequate equilibration of alveolar nitrogen concentration, a necessary assumption for the Haldane transformation, was achieved. Data were analyzed with multivariate (Wilk's Lambda), repeated-measures ANOVA to evaluate effects of treatment (SL, AH, CH) across relative work rates (rest; 25, 50, 75, and 100% $\dot{W}_{max}$; and +O_2). Changes in all variables of interest at absolute work rates of 100 and 175 W were analyzed similarly. Criterion for significance was set at $P < 0.05$. Post hoc, pairwise comparisons were made using the Holm's sequential method to control for type 1 error. Pearson product-moment analyses were used to evaluate relationships between changes in $P_{ET_{CO_2}}$, MCA V_{mean}, and cerebral THb. The intraclass correlation coefficient α was calculated across work rates to assess the test-retest reliability of MCA V_{mean} measurements obtained from a subset of seven subjects during the practice and SL exercise bouts. Data are presented as means ± SD.

RESULTS

Subjects. All 11 subjects participated in each phase of the study, yet 1 subject stopped exercising immediately before the gas switch during HA due to knee pain. Subjects were 21 ± 3 yr old, 176.5 ± 7.5 cm tall, weighed 77.6 ± 12.3 kg, and had thigh skinfold measurements of 12.8 ± 3.6 mm at SL. No significant changes in these variables were measured during AH or CH.

Sea level. $\dot{V}_{O_2}$ increased with work rate until the last 15-s period before the gas switch (<0.01 ml/min increase) (Table 1). During this period, pedal cadence dropped from 82 ± 3 to <60 rpm. After the gas switch, pedal cadence continued to fall,

Table 1. *Values relative to maximal work rate achieved before and after the gas switch to 60% inspired oxygen*

Condition	Power, W	HR, beats/min	$\dot{V}O_2$, l/min	$\dot{V}E$ BTPS, l/min	$\dot{V}E/\dot{V}CO_2$	$P_{ET}CO_2$, Torr	MCA V_{mean}, cm/s	Sp_{O_2}, %	Cerebral Oxygenation			Muscle Oxygenation		
									ΔHbO_2, μM	ΔHHb, μM	ΔTHb, μM	ΔHbO_2, μM	ΔHHb, μM	ΔTHb, μM
Sea Level														
Rest	0	84±8	0.44±0.06	13.6±2.2	36.2±3.9	38.3±3.4	54.8±11.8	98±1	0	0	0	0	0	0
25%	70±7*	107±13*	1.14±0.17*	25.5±3.7*	28.6±2.0*	43.2±3.5*	63.0±12.0*	98±1	−0.3±1.7	0.1±1.2	−0.2±1.1	−3.3±2.2*	2.2±4.0	−1.1±3.2
50%	140±14*	133±13*	1.95±0.19*	46.4±6.6*	25.2±2.4*	43.8±4.4	68.4±15.8*	97±2	1.6±2.1*	−0.3±1.7	1.3±1.7*	−5.5±3.7*	7.0±5.7*	1.5±3.3*
75%	209±21*	161±11*	2.77±0.22*	76.1±14.7*	25.7±3.2	41.5±4.8*	66.6±16.2	98±1	6.5±3.1*	0.7±2.5	7.2±2.9*	−10.53±5.6*	14.7±8.5*	4.2±3.9*
100%	279±27*	187±9*	3.98±0.41*	162.7±24.2*	31.6±4.9*	30.3±4.4*	58.5±13.5*	96±3	5.0±5.8	5.7±5.3*	10.7±4.6*	−12.8±6.5*	17.8±10.3	4.9±5.2
$+O_2$	281±27	188±8	N/A	133±33.2*	N/A	31.8±4.6	52.1±11.4*	97±2*	4.9±6.1	4.2±5.3*	9.1±5.0*	−12.3±6.8	17.9±10.7	5.6±5.5*
Acute Hypoxia														
Rest	0	88±11	0.39±0.08†	13.2±3.5	35.8±4.1	37.7±4.8	55.3±9.1	88±4†	0	0	0	0	0	0
25%	57±7*	116±15*	1.01±0.11*	29.9±4.9*†	31.3±2.3*	38.3±5.5	65.9±11.5*	80±6*	−3.2±3.0*	3.2±2.1*	0.0±3.0	−4.2±2.4*	2.5±4.5	−1.7±3.1
50%	114±14*	136±14*	1.46±0.17*	45.6±8.1*	30.2±2.4*	37.4±4.7	68.8±11.0*	76±5*	−4.3±3.8	5.4±2.6*	1.1±2.3	−9.6±5.5*	10.3±7.1*	0.7±3.0*
75%	171±20*	161±11*	2.03±0.27*	77.4±15.5*	32.1±3.4*	33.8±5.1*	65.9±10.7*	75±6	−3.2±5.1*	7.8±4.5*	4.6±4.4*	−13.9±8.9*	17.4±11.8*	3.5±3.7*
100%	228±27*†	181±7*†	2.73±0.43*†	139.9±34.4*†	40.0±5.1*†	26.0±4.8*†	59.8±7.8*	73±5*†	−3.4±6.5†	11.8±7.3*†	8.3±5.3*	−14.7±8.0	19.6±11.5	4.9±4.0*
$+O_2$	252±30*†	185±7*†	N/A	125.2±30.6*	N/A	27.9±4.7*†	54.8±7.4*	93±8*	10.8±6.4*†	−4.7±6.4*†	6.1±6.2	−10.5±5.7*	15.3±9.3*	4.9±4.2
Chronic Hypoxia														
Rest	0	93±5†	0.45±0.07‡	16.3±3.6†‡	44.7±3.7†‡	32.6±3.3†‡	59.9±15.1	87±4†‡	0	0	0	0	0	0
25%	59±6*	120±9*	1.17±0.10*	36.4±4.7*	39.3±3.0*	31.8±3.0*	69.1±17.1*	82±6*	−3.9±1.2*	3.7±1.4*	−0.2±0.9	−4.0±3.1*	3.3±2.5*	−0.7±3.3
50%	118±12*	135±8*	1.75±0.21*	57.8±11.0*	38.6±3.1*	30.7±2.8*	70.5±16.9	79±6*	−5.9±2.5*	7.1±2.5*	1.3±2.0*	−9.2±5.3*	10.2±5.5*	1.0±1.0*
75%	177±18*	160±6*	2.45±0.22*	97.0±16.7*	41.4±4.1*	26.8±3.1*	70.5±16.2	76±5*	−6.6±3.5	11.1±4.0*	4.5±4.0*	−12.7±5.9*	16.1±7.4*	3.4±3.5*
100%	237±23*†	176±5*†‡	3.16±0.40*†‡	163.6±34.3*‡	49.6±5.4*†‡	21.6±2.5*†‡	65.9±11.7*†	74±4*†	−9.6±5.4*††	17.2±8.7*†‡	7.6±7.9*	−14.8±5.5*	18.7±8.5*	3.9±5.5
$+O_2$	276±39*‡	183±3*†	N/A	148.9±30.3*	N/A	23.8±4.2*†‡	57.6±13.1*	93±8*	4.4±9.0*‡	1.0±11.0*‡	5.4±7.4	−11.7±5.2*	14.8±7.6*	3.2±4.8

Values are means ± SD. 25–100%, Percent maximal work rate before gas switch; $+O_2$, exhaustion after gas switch; power, cycling power; HR, heart rate; $\dot{V}O_2$, oxygen consumption; $\dot{V}E$, expired ventilation; $\dot{V}E/\dot{V}CO2$, ventilatory equivalents of carbon dioxide; $P_{ET}CO_2$, partial pressure of end-tidal carbon dioxide; MCA V_{mean}, middle cerebral artery mean blood flow velocity; Sp_{O_2}, arterial oxygen saturation from pulse oximetry; ΔHbO_2, ΔHHb, and ΔTHb, changes from resting baseline values (0 μM) of oxy-, deoxy-, and total hemoglobin, respectively. *Different from previous work rate ($P < 0.05$). Differences between conditions were tested at rest, 100% peak work rate, and $+O_2$ only: †different from sea level, ‡different from acute hypoxia ($P < 0.05$).

despite strong verbal encouragement, and the test was terminated when pedal rpm dropped below 50, <10 s later.

Oxygenation of the vastus lateralis was progressively reduced during incremental exercise up to 75% $\dot{W}_{max}$, but demonstrated a plateau thereafter (Table 1). In contrast, cerebral oxygenation rose from rest through moderate-intensity exercise, likely due to vasodilation (increased HbO_2, THb, $P_{ET}CO_2$, and MCA V_{mean}), but fell from 75 to 100% $\dot{W}_{max}$ (decreased $P_{ET}CO_2$ and MCA V_{mean} and increased HHb and THb). Following the gas switch, cerebral THb decreased, and muscle THb increased, suggesting cerebral vasoconstriction and muscle vasodilation.

The correlation between $P_{ET}CO_2$ and MCA V_{mean} was significant at low work rates, as both variables increased ($R^2 = 0.72$; slope = 1.8 cm·s^{-1}·Torr^{-1}), but was stronger above 50% $\dot{W}_{max}$, as both variables decreased ($R^2 = 0.91$; slope = 0.79 cm·s^{-1}·Torr^{-1}) (Fig. 1). Changes in cerebral blood volume (THb) were correlated with changes in MCA V_{mean} ($r = 0.61$) up to 75% $\dot{W}_{max}$ (Fig. 2). From 75 to 100% $\dot{W}_{max}$, correlations of MCA V_{mean} and $P_{ET}CO_2$ with THb displayed inverse relationships ($r = -0.86$ and $r = -0.85$, respectively).

Test-retest measurements of resting MCA V_{mean} measurements obtained during the practice and SL bouts yielded a coefficient of variation of 4.87%. This statistic incorporates daily variation in MCA V_{mean} and accuracy in replacement of the transcranial Doppler probe. The intraclass correlation coefficient α calculated across work rates was 0.91, indicating that the pattern of change in MCA V_{mean} was consistent between bouts.

Acute hypoxia. $\dot{W}_{max}$ and maximum $\dot{V}O_2$ ($\dot{V}O_{2max}$) achieved during AH were 18 ± 6 and 31 ± 8% lower, respectively, than SL. However, following the gas switch, 8 of 11 subjects were able to immediately increase pedal cadence from <60 to 82 ± 10 rpm and continue for an average of 96 ± 61 s. The increased cycling time resulted in an 11% increase in power, ending at 89 ± 4% of SL $\dot{W}_{max}$.

The extent of muscle deoxygenation was greater at each absolute work rate (Table 2), yet the pattern of deoxygenation

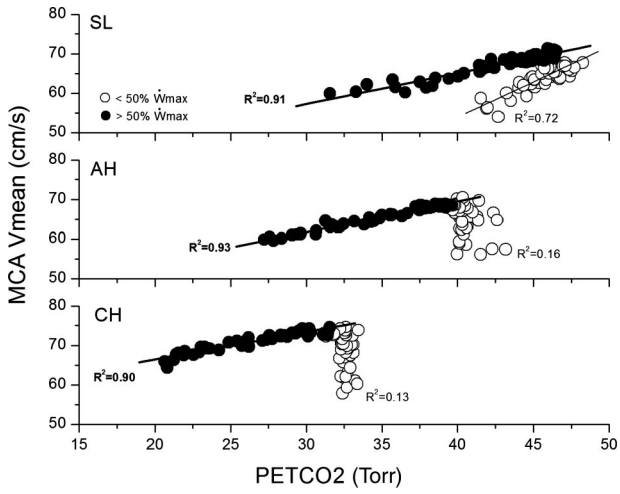

Fig. 1. Scatterplots showing relationships between middle cerebral artery mean blood flow velocity (MCA V_{mean}) and partial pressure of end-tidal carbon dioxide ($P_{ET}CO_2$) across work rates. At sea level (SL), the correlation is strong at low work rates, but becomes markedly stronger above 50% maximal work rate ($\dot{W}_{max}$). During acute hypoxia (AH) and chronic hypoxia (CH), the correlations are weak at low work rates, but become strong above 50% $\dot{W}_{max}$.

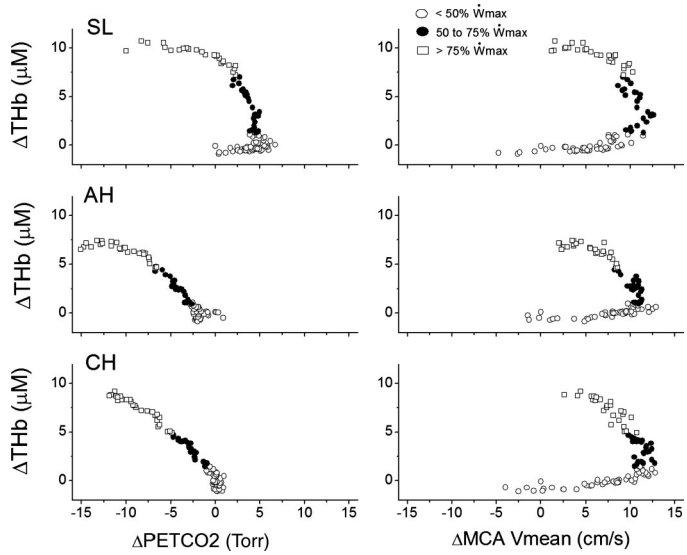

Fig. 2. Scatterplots showing relationships between changes (Δ) in regional cerebral blood volume (THb) and both $P_{ET}CO_2$ and MCA V_{mean}. Correlations are weak at low work rates, but display strong inverse relationships above 75% $\dot{W}_{max}$, indicating that frontal lobe blood volume increases with work rate, despite reductions in $P_{ET}CO_2$ and MCA V_{mean}.

observed across relative work rates was similar to that at SL (Fig. 3), with no differences between any muscle NIRS values at $\dot{W}_{max}$. After the gas switch, muscle HbO_2 increased (29 ± 11% return to baseline) and HHb decreased (23 ± 11% return to baseline) without a change in THb.

Cerebral oxygenation fell throughout exercise until $\dot{W}_{max}$. Cerebral HbO_2 was less and HHb was greater than SL at all absolute and relative work rates, while THb remained similar between conditions. Following the gas switch, cerebral oxygenation increased as HbO_2 rose (275 ± 174% return to baseline) and HHb fell (192 ± 116% return to baseline) without a change in THb.

The relationship between $P_{ET}CO_2$ and MCA V_{mean} was significant between 50 and 100% $\dot{W}_{max}$ ($R^2 = 0.93$; slope = 0.78 cm·s^{-1}·Torr^{-1}) (Fig. 1). Correlations between cerebral THb and MCA V_{mean} were $r = 0.71$ (<50% $\dot{W}_{max}$), $r = -0.11$ (50–75% $\dot{W}_{max}$), and $r = -0.78$ (75–100% $\dot{W}_{max}$) (Fig. 2). Correlations between cerebral THb and $P_{ET}CO_2$ were $r = -0.37$ (<50% $\dot{W}_{max}$), $r = -0.95$ (50–75% $\dot{W}_{max}$), and $r = -0.81$ (75–100% $\dot{W}_{max}$) (Fig. 2).

Chronic hypoxia. $\dot{W}_{max}$ and $\dot{V}O_{2max}$ were 15 ± 5 and 21 ± 6% lower, respectively, than SL, but 4 ± 6 and 16 ± 8% greater than AH. Following the gas switch, 9 of the 10 subjects completing the protocol were able to increase pedal cadence from <60 to 88 ± 11 rpm and continue cycling for 162 ± 90 s. The increased cycling time resulted in a 17% increase in power, ending at 97 ± 7% of SL $\dot{W}_{max}$.

Muscle oxygenation followed a nearly identical pattern to that seen in AH (Fig. 3). The extent of deoxygenation was greater than SL at each absolute work rate, but not different from AH. Expressed relative to SL $\dot{W}_{max}$, there were no differences in muscle oxygenation between the three conditions at any work rate. After the gas switch, muscle oxygenation increased as HbO_2 rose (31 ± 25% return to baseline) and HHb fell (30 ± 25% return to baseline) without a change in THb.

Table 2. *Values at absolute work rates*

Condition	HR, beats/min	$\dot{V}_{O_2}$, l/min	$\dot{V}_{E\ BTPS}$, l/min	$\dot{V}_E/\dot{V}_{CO2}$	$P_{ET_{CO_2}}$, Torr	MCA V_{mean}, cm/s	S_{PO_2}, %	Cerebral Oxygenation			Muscle Oxygenation		
								ΔHbO_2, μM	ΔHHb, μM	ΔTHb, μM	ΔHbO_2, μM	ΔHHb, μM	ΔTHb, μM
Sea Level													
Rest	84±8	0.45±0.06	13.6±2.2	36.2±3.9	38.3±3.4	54.8±11.8	98±1	0	0	0	0	0	0
100 W	117±13	1.55±0.17	33.6±4.8	26.4±1.8*	46.8±4.9*	65.6±14.7*	98±1	−0.1±2.1	0.1±1.5	0.0±1.0	−3.0±3.1*	2.5±4.6	−0.5±2.9
175 W	149±15*	2.52±0.34*	60.9±11.7*	25.0±3.0*	45.4±6.2	65.2±17.2	98±2	4.7±3.0*	−0.3±2.2	4.4±2.5*	−7.4±5.5*	10.6±7.3*	3.2±3.5*
Acute Hypoxia													
Rest	88±11	0.39±0.08†	13.2±3.5	35.8±4.1	37.7±4.8	55.3±9.1	88±4†	0	0	0	0	0	0
100 W	131±16*†	1.33±0.13*†	40.8±5.8*†	30.4±2.3*†	40.8±7.9*†	62.9±21.1*	76±7*†	−4.2±4.2*†	5.0±2.5*†	0.7±3.0	−8.3±5.6*†	8.4±7.8*†	0.1±3.2
175 W	164±12*†	2.10±0.16*†	83.1±11.8*†	33.0±3.3*†	35.0±6.3*†	65.7±9.3	75±6†	−3.0±5.2†	7.6±4.7*†	4.6±3.5*	−14.0±8.7*†	17.7±12.2*†	3.7±4.0*
Chronic Hypoxia													
Rest	93±5†	0.45±0.06‡	16.3±3.6†‡	44.7±3.7†‡	32.6±3.2†‡	59.9±15.0	87±4†‡	0	0	0	0	0	0
100 W	128±7*†	1.54±0.10*‡	48.8±6.6*†	38.6±3.0*†‡	32.1±3.0†‡	71.6±17.7*	78±8*†	−5.0±2.3*†	6.1±2.0*†	1.1±1.8	−8.1±5.4*†	9.2±7.5*†	1.2±4.2
175 W	160±9*†‡	2.42±0.14*‡	97.6±13.4*†‡	41.9±3.3*†‡	27.9±3.6*†‡	72.0±15.2†‡	75±8*†	−6.6±3.5*†‡	11.1±3.7*†‡	4.5±3.4*	−14.3±8.5*†	19.4±13.1*†	5.1±5.9*

Values are means ± SD. *Different from previous work rate, †different from sea level, ‡different from acute hypoxia ($P < 0.05$).

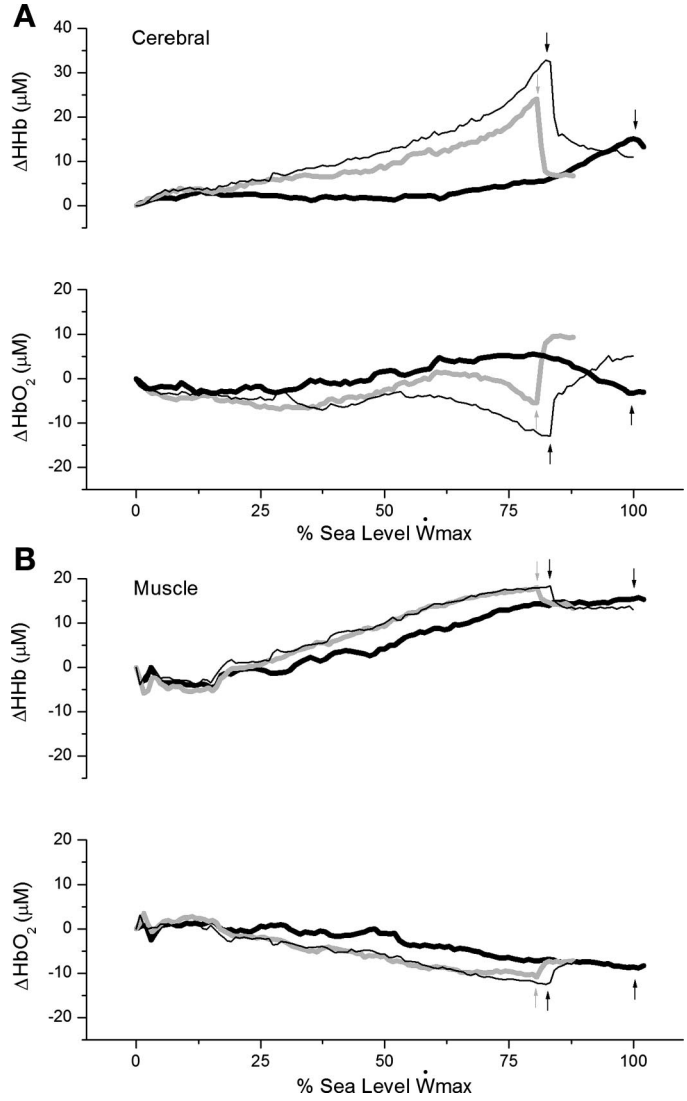

Fig. 3. Representative changes in cerebral (*A*) and muscle (*B*) oxyhemoglobin (HbO_2) and deoxyhemoglobin (HHb) from a single subject performing incremental exercise to maximal exertion at SL (thick solid line), AH (thick shaded line), and CH (thin solid line). Arrows mark the gas switch to 60% inspired oxygen. The subject could not continue exercise after the gas switch at SL; however, during the hypoxic trials, the gas switch improved cerebral oxygenation and maximal exercise performance by 9 and 20% in AH and CH, respectively.

Cerebral oxygenation also followed a similar overall pattern to that seen during AH (Fig. 3), although the extent of deoxygenation, as indicated by increased HHb and decreased HbO_2, was significantly greater than AH at $\dot{W}_{max}$. Cerebral oxygenation following the gas switch improved as HbO_2 increased (192 ± 208% return to baseline) and HHb decreased (111 ± 64% return to baseline), while THb was unchanged.

The relationship between $P_{ET_{CO_2}}$ and MCA V_{mean} was significant >50% $\dot{W}_{max}$, but the slope was reduced compared with SL and AH ($R^2 = 0.90$; slope = 0.69 cm·s^{-1}·Torr^{-1}) (Fig. 1). Correlations between cerebral THb and MCA V_{mean} were r = 0.82 (<50% $\dot{W}_{max}$), r = 0.33 (50–75% $\dot{W}_{max}$), and $r = -0.85$ (75–100% $\dot{W}_{max}$) (Fig. 2). $P_{ET_{CO_2}}$ was inversely related to THb <50% $\dot{W}_{max}$ ($r = -0.62$), between 50 and 75% $\dot{W}_{max}$ ($r = -0.97$), as well as from 75 to 100% $\dot{W}_{max}$ ($r = -0.96$) (Fig. 2).

DISCUSSION

Our data describe differences in cerebrovascular responses to incremental exercise in normoxia and during acute and chronic exposures to hypobaric hypoxia. The results support the hypothesis that changes in cerebral oxygenation influence maximal exercise performance during hypobaric hypoxia.

Cerebrovascular responses to incremental exercise. At low-to-moderate exercise intensities (<75% $\dot{W}_{max}$) in normoxia, increases in cerebral oxygenation and regional cerebral blood volume (increased HbO_2 and THb) were associated with simultaneous increases in $P_{ET}CO_2$ and MCA V_{mean}. A reasonable explanation for this is that exercise-induced elevation of Pa_{CO_2} results in cerebral vasodilation, increased cerebral blood flow, and augmented cerebral oxygenation; however, the shared variance between these variables was <36%. It is thus probable that other local factors that affect vascular tone, such as adenosine (50), potassium (17, 18), reactive oxygen and nitrogen species (16), and/or autonomic function (49), influence cerebral blood flow and oxygenation during normoxic exercise.

The relationship between $P_{ET}CO_2$ and MCA V_{mean} during low work rates was strong, but was distinctly stronger from moderate to high (75–100% $\dot{W}_{max}$) work rates. Others have reported similar changes in cerebrovascular reactivity from rest to moderate work rates (38), yet such a distinct breakpoint in reactivity (Fig. 1), associated with a switch from rising to falling $P_{ET}CO_2$ and MCA V_{mean}, has not been described during continuous incremental exercise. Support for a relative independence between Pa_{CO_2} and cerebral blood flow, which may explain the weaker $P_{ET}CO_2$-to-MCA V_{mean} correlations at low work rates observed in the present study, has been provided by studies demonstrating a strong association between cerebral blood flow and cardiac output during submaximal exercise (25, 26, 39). Specifically, Ogoh et al. (38) showed that increases in cardiac output were largely responsible for augmented cerebral blood flow during low-intensity exercise (50% $\dot{V}O_{2max}$).

At high work rates, changes in $P_{ET}CO_2$ and MCA V_{mean} were inversely correlated with changes in THb, indicating that decreased MCA V_{mean} was accompanied by increased frontal cortex blood volume. This seemingly paradoxical finding emphasizes the regional specificity of cerebrovascular regulation (20). We propose that, during high-intensity exercise, decreased cerebral blood flow, coupled with a slight increase in metabolic demand (13), results in relative cerebral hypoperfusion, which, in turn, stimulates parasympathetic-induced vasodilation (28). Since venous vessels hold 70–80% of cerebral blood volume (42), cerebrovasodilation is reflected primarily by increases in HHb and THb, as seen from 75–100% $\dot{W}_{max}$.

During AH, relationships between $P_{ET}CO_2$ and MCA V_{mean} were weak across low work rates, as MCA V_{mean} increased while $P_{ET}CO_2$ remained stable. Similar findings in cerebrovascular reactivity have been reported (1, 27) and may be explained by the direct influence of increased cardiac output on cerebral blood flow (25, 26, 38). At moderate and high work rates, the $P_{ET}CO_2$ and MCA V_{mean} relationship was restored to a linear relationship as $P_{ET}CO_2$ began to fall. Following acclimatization, the slope of the relationship was reduced, indicating that cerebrovascular reactivity was decreased during moderate- and high-intensity exercise. This compensatory effect attenuated hypocapnic-mediated reduction in cerebral blood flow during the ventilatory acclimatization period.

Cerebral hypoxia and exercise performance. This study adds support to the theory that cerebral deoxygenation during exercise poses a limitation to maximal exercise performance in hypoxia (7, 8, 30, 36, 37). Direct cerebrovascular evidence for this hypothesis has been limited to studies in AH of isolated, small muscle mass activity (40) and submaximal cycling to exhaustion (4). Our incremental cycling protocol expands the range of knowledge to encompass maximal intensity exercise in AH and CH.

Our results are similar to those of Amann et al. (4), who showed that physical fatigue during acute exposure to severe hypoxia ($F_{I_{O_2}}$ 0.10; $P_{I_{O_2}}$ 69 Torr; Sp_{O_2} ~67%) was largely influenced by central factors (outside the muscle), since a rapid switch to a hyperoxic inspirate ($F_{I_{O_2}}$ 0.60) improved cerebral oxygenation (NIRS) and exercise time to exhaustion, in the absence of a critical level of peripheral muscle fatigue (2, 3, 29, 41). Because muscle factors appeared to exert a dominant influence in determining fatigue during normoxia ($F_{I_{O_2}}$ 0.21; $P_{I_{O_2}}$ 145 Torr; Sp_{O_2} ~94%) and at moderate levels of hypoxia ($F_{I_{O_2}}$ 0.15; $P_{I_{O_2}}$ 104 Torr; Sp_{O_2} ~82%), the authors proposed that central factors, such as cerebral hypoxia, play a predominant role in fatigue when exercise elicits Sp_{O_2} values >70–75%, associated with a $P_{I_{O_2}}$ between 69 and 104 Torr. In the present study, switching to a hyperoxic inspirate ($F_{I_{O_2}}$ 0.60) was associated with increased performance during Acute hypoxic exposures and CH ($P_{I_{O_2}}$ 86 Torr) when Sp_{O_2} at maximal intensity was <75%.

During the late stages of exercise at SL, subjects exhibited signs of relative cerebral deoxygenation, yet the magnitude of cerebral hypoxia was unlikely to limit performance (46). Muscle deoxygenation may also have influenced the sensation of fatigue, but the data show a stable relationship between muscle oxygen delivery and consumption from 75 to 100% $\dot{W}_{max}$, suggesting that muscle oxygenation was not at a critically low level. Following the gas switch at SL, subjects' pedal cadence continued to fall, taking <10 s to drop below the minimal cadence criteria of the test (50 rpm). The short period of hyperoxia ($F_{I_{O_2}}$ 0.60) was associated with a slight improvement in arterial saturation, but no increase in cerebral or muscle oxygenation, given that there were no changes in HbO_2. The lack of significant improvement in oxygenation supports the contention that the extent of tissue deoxygenation experienced during normoxia was not a limiting factor (21, 46). We believe it is more likely that subjects were limited by other factors, such as intramuscular accumulation of inorganic phosphosphate (24), which ultimately decreased central motor drive (2).

The magnitude of cerebral deoxygenation during hypoxic exposures was more likely to have affected efferent motor drive and exercise performance (2). A link between cerebral hypoxia and motor performance has been proposed (4), in which reduced neurotransmitter turnover rates affect limbic to motor communication in the basal ganglia (33), thus influencing motivation (43, 44) and movement (12). It may thus be argued that, because the gas switch increased cerebral oxygenation to levels above that seen at rest, the influence of cerebral hypoxia on fatigue was completely alleviated, and subjects were able to continue exercise. The fact that subjects were able to continue cycling until they reached approximately the same $\dot{W}_{max}$ achieved in normoxia suggests that peripheral muscle factors may have been responsible for the sensation of exhaustion at the end of exercise in hyperoxia (4).

Changes in muscle oxygenation following the gas switch are less likely to explain the results, since the effect on performance was too quick to have been mediated via a reduction in the accumulation of factors associated with peripheral muscle fatigue (4, 31). Similarly, muscle oxygenation was only partially restored to a new plateau, representing a continuing balance between oxygen delivery and consumption, which was maintained, despite increased work rates.

These findings illustrate an association between cerebral oxygenation and maximal exercise performance during acute hypoxic exposures ($P_{I_{O_2}}$ 86 Torr; Sp_{O_2} <75%), but do not imply a cause-and-effect relationship. Because fatigue is a perception, it is likely to be influenced by many sensory inputs; thus the increase in performance may have been moderated by other oxygen-sensing tissues, such as peripheral chemoreceptors or even the pulmonary vasculature (22). Alternatively, increased heart rate during hyperoxia raises the possibility that exercise before the gas switch may have been limited, at least in part, by a hypoxia-induced limitation to cardiac output (10, 11). While switching from acute hypoxia to hyperoxia does not affect heart rate when work rate remains constant (4), heart rate may continue to rise if work rate is increased (10). In the present study, peak heart rate before the gas switch was lower in CH than AH, yet maximal heart rate during hyperoxia was not different between conditions. This suggests that parasympathetic-imposed limitations on cardiac output (8) may exert a greater influence on fatigue during CH.

The first hypoxic test was performed in a hypobaric chamber after ~20 min of resting exposure. The time before testing falls within the time frame for the expected acute hypoxic ventilatory response, but precludes more pronounced ventilatory acclimatization. The second hypoxic test was performed after 5 days of acclimatization to moderate altitude (2,200 m: $P_{I_{O_2}}$ 115 Torr) and 24 h of exposure to high altitude (4,300 m; $P_{I_{O_2}}$ 86 Torr). This second approach was expected to elicit partial ventilatory acclimatization. Subjects' ventilatory responses at $\dot{W}_{max}$ were, in fact, greater at CH (higher minute ventilation, lower $P_{ET_{CO_2}}$ vs. AH). Higher ventilation rates might explain the differences in cerebral oxygenation, if hypocapnic vasoconstriction reduced cerebral blood flow and increased the extent of relative hypoperfusion, yet MCA V_{mean} near $\dot{W}_{max}$ was greater in CH. This finding may be explained by the reduction in cerebrovascular reactivity during moderate and high intensities, which attenuated hypocapnic vasoconstriction. We believe it is likely that the greater cerebral deoxygenation seen at high altitude was related to elevated cerebral metabolic rates, since data from the highest absolute work rate achieved by all subjects during hypoxia (175 W) showed greater cerebral oxygen consumption (lower HbO_2, higher HHb, similar THb) during CH. Combined effects of differences in cerebrovascular responses and cerebral metabolism can explain the variations seen during AH and CH.

Limitations. The continuous-wave NIRS technique used in this study measures relative changes in cerebral oxygenation from an arbitrary starting point. Since the differential path length factors were estimated, absolute NIRS measurements and tissue saturation values during each condition were not measurable. Consequently, the absolute effect of acclimatization on tissue oxygenation remains to be determined. Also, we acknowledge the fact that frontal lobe oxygenation is a regional measurement that may not be reflective of global cerebral oxygenation during exercise, as more active regions of the brain may receive a greater proportion of blood flow (14). Future studies that interrogate multiple regions of the brain are needed to gain a clearer understanding of cerebrovascular responses to exercise and their relationships with fatigue.

Conclusions. Hypobaric hypoxia affects cerebrovascular responses to incremental exercise and results in cerebral deoxygenation at maximal intensity. Cerebral oxygenation appears to be an important variable influencing fatigue under hypobaric hypoxic ($P_{I_{O_2}}$ 86 Torr), since reversal of cerebral deoxygenation at maximal exertion was associated with increased performance.

ACKNOWLEDGMENTS

We express our sincere gratitude to Stephen Muza of the USARIEM, and Michael Zupan, Michael Brothers, and Brandon Doan of the US Air Force, whose efforts made the experiments possible. Additionally, we are indebted to Paul Rock of Oklahoma State University for providing continuous medical supervision on Pike's Peak.

GRANTS

Major funding was provided the US Army Medical Research and Materiel Command, Army Technical Objective IV.MD.2006-01. Additional funding was provided by the University of Colorado at Colorado Springs Center for Research and Creative Work, and the Altitude Research Center, University of Colorado at Denver and Health Sciences Center.

DISCLAIMER

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Army or the Department of Defense. The investigators have adhered to the policies for protection of human subjects as prescribed in Army and US Army Medical Research & Materiel Command Regulations 70-25, and the research was conducted in adherence with the provisions of 45 CFR Part 46. Human subjects participated in these studies after giving their free and informed voluntary consent.

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